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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,298	05/20/1999	CHING-LEOU TENG	ISIS-3510	6350

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/315,298	TENG ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *15 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,13,20,80,84,85,91 and 95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,13,20,80,84,85,91 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicant's arguments with respect to claims 1, 4-7, 13, 19-20, 80, 84-85, 91, and 95 have been considered but are moot in view of the new ground(s) of rejection.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

3. Claims 1, 5, 13, 91 and 95 are rejected under 35 U.S.C. 102(e or b) as being anticipated by Yiv US 5707648 A; or WO 95/14037 (see entire contents of each document; citations are give for the US Patent.)

Yiv discloses drug delivery compositions that contain an oil or lipid (hydrophobic) phase, an aqueous (hydrophilic) phase, and a surfactant or mixture of surfactants, and an active agent, preferably biologically active. The drug delivery compositions are optimized for use in conjunction with capsules for oral, rectal, and vaginal, preferably oral and rectal, and more preferably oral, administration. The compositions of Yiv can be administered by any method such as parenteral, enteral, and any other mucousal means and without a capsule container. (See col. 3, lines 46-56).

The delivery compositions of Yiv are described as multi-component systems that are preferably transparent, thermodynamically stable solutions resembling swollen micelles and w/o microemulsions, however the particle size of the present compositions may not fall within the ranges commonly understood to encompass micelles and microemulsions. (See col. 4, lines 10-19). The drug delivery compositions preferably comprise, a fatty acid, see col. 4-5.

The drug delivery compositions of Yiv can be formulated with agents for enhancing mucosal absorption of biologically active agents. These include bile salts such as trihydroxy bile salts, i.e. cholate, taurocholate, and glycocholate, dihydroxy bile salts, i.e. deoxycholate, taurodeoxycholate, chenodeoxycholate, and ursodeoxycholate, triketo bile salts such as dehydrocholate. (See col. 12, lines 56-67).

Suitable active agents encompassed by the Yiv invention include nucleosides, nucleotides and their polymers. Suitable nucleosides include 3'-azido-3'-deoxythimidine, 2',3'-dideoxy-derivatives of adenosine, cytidine, inosine, thymidine or guanosine. Suitable polynucleotides include antisense nucleotides having 3 to 30 nucleotide bases with nucleotide sequences complimentary to those coding for viral proteins or RNA's, oncogene proteins or RNA's, or inflammatory proteins or RNA's. Also useful are polynucleotides having 3 to 30 bases capable of forming triple helix structures with the DNA coding for the above. (See col. 12, lines 20-31)

Claim Rejections - 35 USC § 103

4. Claims 1, 4-7, 13, 19-20, 80, 84-85, 91, and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kawai et al. in view of Yiv (US 5707648 A; or WO 95/14037), Bennett et al. (US Patent No. 5,514,788) and Nielsen et al.

Kawai et al. disclose lipid microsphere in fat emulsion as a carrier to transducing gene DNA (i.e., microemulsion). These compositions comprise at least a transducing gene DNA, wherein said transducing gene DNA is synthetic oligonucleotide, such as the so-called phosphorothioate type, or it is a structural gene integrated into a vector (page 13, last paragraph of Japanese translation). Moreover, the compositions of the Kawai et al. invention comprise a transducing-gene DNA; fat emulsion base of at least one kind chosen from a vegetable oil,

triglyceride of the medium chain triglyceride of 8-12 carbon atoms (such as capric, lauric and caprylic acid, see page 16, paragraph [0013]), fatty acids of 6-18 carbon atoms (penetration enhancer); the emulsifier of at least one kind chosen from a phospholipid and a nonionic surface active agent; a cholesterol derivative; and water (see summary of the invention, page 3 of the Japanese translation). It is assumed from the reference that the emulsions are oil-in water emulsions since they are described in the Japenese translation as being fat emulsions wherein the water serves as the solvent (page 18, paragraph [0016] of translation).

The "transducing-gene DNA" of Kawai et al. is chosen from cancer suppression gene DNA, gene DNA of an interleukin-1, interleukin-2, interleukin-4, interleukin-6, interleukin-7, GM-CSF, TNF-alpha, interferon-c, PDGF (cell adhesion protein), HVS-tk, diptheria-toxin A, and cytosine deaminases (see 3rd paragraph of page 5, Japanese translation).

In another embodiment of Kawai et al., an emulsifier is distributed above the fat emulsion, wherein the emulsifier is a phospholipid or a nonionic surface-active agent (page 17, paragraph [0015]).

Moreover, the fat emulsions of Kawai et al. can be made to contain further additive agents, such as an isotonizing agent emulsification support agent, a stabilizer (for example, wherein said stabilizer is dextran see page 20, paragraph [0020]), and a pH manufacture agent (page 18, paragraph [0017]).

However, Kawai et al. does not disclose emulsions comprising a bile salt, wherein said bile salt is selected from the group consisting of: cholic acid, dehydrocholic acid, deoxycholic acid, glucholic acid, glycholic acid, glycodeoxycholic acid, taurodeoxycholic acid, chenodeoxycholic acid, ursodeoxycholic acid, sodium tauro-24,25-dihydrofusidate, sodium

glycodihydrofusidate, polyoxyethylene-9-lauryl ether. Neither does Kawai et al. disclose compositions comprising an oligonucleotide wherein said oligonucleotide is selected from the group consisting of SEQ ID NO: 1, 2, 48-50, 16, 19, and 51-54.

Yiv teaches that drug delivery compositions (which comprise and aqueous and an oily phase) can be formulated with bile salts in order to enhance mucosal absorption of the drug. These include bile salts such as trihydroxy bile salts, i.e. cholate, taurocholate, and glycocholate, dihydroxy bile salts, i.e. deoxycholate, taurodeoxycholate, chenodeoxycholate, and ursodeoxycholate, triketo bile salts such as dehydrocholate. (See col. 12, lines 56-67).

Bennett et al. discloses antisense oligonucleotide compositions and formulations that can be administered topically, orally, by inhalation, parenterally, subcutaneous, intraperitoneal, or intramuscular injection. Formulations for topical administration may include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms or gloves may also be useful. Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be desirable. Formulations for parenteral administration may include sterile aqueous solutions which may also contain buffers, liposomes, diluents and other suitable additives. (Col. 7, lines 44-65). The compositions of Bennett et al. may comprise the ISIS-2303 oligonucleotide (See Table 1, SEQ ID NO: 22), this oligonucleotide is identical in sequence to SEQ ID NO: 1 of the instant invention.

Nielsen et al. discloses pharmaceutical compositions that are intended for application to or through the mucosa of an animal, wherein the mucosa is preferably selected from oral, nasal, vaginal, rectal, aural, lung, and gastrointestinal mucosa (page 3, lines 4-8) . In one embodiment of the Nielsen et al. invention, the pharmaceutical composition comprises a biologically active substance, wherein said substance is ISIS-2922 (page 14, lines 19-22), which is an anti-herpes virus agent that is a phosphorothioate modified antisense oligonucleotide according to SEQ ID NO: 48 of the instant application (see also the Registry report of the sequence of ISIS-2922).

The compositions of Nielsen et al. that are specifically for oral administration may comprise pharmaceutically acceptable carriers or excipients, which may include (*inter alia*) penetration enhancers, ointment bases, excipients, emulsifying agents (i.e. forming an emulsion), and chelating agents (page 22, lines 5-12). The compositions or formulations of Nielsen et al. may also comprise emulsions, see page 21, lines 4-8, The ointment bases of Nielsen et al. include fatty acids such as vegetable oils, and palmitate (page 23, lines 9-11).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Kawai et al., Yiv, Bennett et al. and Nielsen et al. to make the claimed invention. Absent any evidence of unexpected results associated with the claimed compounds, it would have been obvious to one of ordinary skill in the art at the time of filing to modify the compositions of Kawai et al. to further comprise bile salts, or to comprise the oligonucleotides disclosed in Bennett et al. and Nielsen et al. One of ordinary skill in the art would have been motivated to make this modification since the compositions of Kawai et al. are intended to provide carriers suitable for transducing gene DNA associated with cancer suppression genes, and DNA relevant to viral illness, and the antisense oligonucleotides of

Bennett et al. and Nielsen et al. are disclosed as being useful for inhibiting the expression of genes associated with cancer (see col. 5, lines 45-47 of Bennett et al.) and viral infection (see abstract of Nielsen et al.), respectively. Moreover, one of ordinary skill in the art would have been motivated to modify the compositions of Kawai et al. with the bile salts of Yiv for the expressed benefits of the presence of bile salts in pharmaceutical compositions according to Yiv, specifically wherein the bile salts function to improve mucosal absorption of biologically active materials.

Therefore, the invention as a whole would have been *prima facie* obvious over Kawai et al. in view of Bennett et al., Yiv and Nielsen et al.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Janet L. Epps-Ford, Ph.D.
Patent Examiner
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JLE